

# Optimizing Efficiency of Perturbative Monte Carlo Method

TOM J. EVANS, THANH N. TRUONG

Department of Chemistry, University of Utah, Salt Lake City, Utah 84112

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**ABSTRACT:** We introduce error weighting functions into the perturbative Monte Carlo method for use with a hybrid *ab initio* quantum mechanics/molecular mechanics (QM/MM) potential. The perturbative Monte Carlo approach introduced earlier provides a means to reduce the number of full SCF calculations in simulations using a QM/MM potential by evoking perturbation theory to calculate energy changes due to displacements of an MM molecule. The use of weighting functions, introduced here, allows an optimal number of MM molecule displacements to occur between the performance of the full self-consistent field calculations. This will allow the *ab initio* QM/MM approach to be applied to systems that require more accurate treatment of the QM and/or MM regions. © 1998 John Wiley & Sons, Inc. J Comput Chem 19: 1632–1638, 1998

**Keywords:** Monte Carlo simulation; QM/MM method; Perturbation theory; microsolvation

## Introduction

The vast majority of reactions that are of interest to chemists are those that occur in the condensed liquid phase, where interactions with the solvent can play a significant role in influencing the behavior of molecules as well as the reactions in which they participate. Theoreticians face

special challenges as they attempt to model these condensed-phase chemical reactions. Quantum-mechanical (QM) methods have existed for some time that are capable of answering, in a quantitative way, questions concerning condensed-phase processes.<sup>1,2</sup> However, even the least computationally demanding of these methods is still far too expensive for the large number of molecules that need to be included in a calculation involving the liquid phase.

Computational methods have been introduced that allow for a less rigorous, albeit computationally achievable, study of condensed-phase sys-

Correspondence to: T. N. Truong; e-mail: truong@mercury.chem.utah.edu

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tems. One common methodology is the use of empirical molecular mechanical (MM) force fields in molecular dynamics (MD) and Monte Carlo (MC) simulations.<sup>3–5</sup> In spite of the approximations included in these empirical functions, valuable insight into the interactions that occur between molecules in solution has been obtained. However, the use of MM force fields has shortcomings. Current MM force fields are not capable of representing the interactions that constitute the very nature of a chemical reaction, specifically, the large changes in electron density which occur during chemical bond breaking and forming.

Recently, a general method has been introduced that shows promise when used to investigate condensed-phase reactions. By combining QM and MM techniques, it's possible to perform calculations on atoms or molecules, which have a QM representation, in the field of MM molecules that represent the solvent environment. These combined QM/MM methods<sup>6–9</sup> allow for a reduction in computational cost relative to standard QM methods, while allowing for the investigation of chemical reactions and polarization effects in solution.

The QM portion of the solution may be represented using an *ab initio* molecular orbital (MO) representation. These calculations can be systematically improved by using larger basis sets or more accurate, correlated methods.<sup>1,2</sup> However, most applications of QM/MM methods use a semiempirical representation of the QM region. These have been used extensively to investigate solvated systems, as well as for studying large molecules of biological interest.<sup>10</sup> This is due to the large number of electronic structure calculations required for sufficient sampling of the configuration space using conventional MC or MD methods. Semiempirical MO methods are very useful, however, they do have many limitations. For instance, they cannot be used for systems for which parameters do not exist, and their accuracy for modeling chemical reactions is often questionable. Thus, it is desirable to treat the QM region at an *ab initio* MO or DFT level.

In a typical MC sampling procedure, only one atom or molecule is displaced at each Monte Carlo step. This differs from MD simulations where all the atoms or molecules of the system are moved with the solution of Newton's equations at each time increment. For the displacement of a solvent molecule in a MC simulation that does not have a large effect on the solute wave function, it is possible to calculate the corresponding energy change

using the wave function from the previously accepted MC step without the need of performing a full self-consistent field (SCF) calculation again. This will significantly reduce the number of SCF calculations required. This method is called perturbative MC by Truong and Stefanovich,<sup>11,12</sup> and has been employed in studies using AM1/MM<sup>13</sup> as well as DFT/MM-coupled potentials.<sup>14</sup>

It is possible to further increase the efficiency associated with the perturbative MC method by introducing error weighting functions that will allow for an optimal number of MM solvent displacements between the performance of the QM portion of the simulation in a controlled manner. Due to the fact that most of the computational demand associated with a combined QM/MM simulation is associated with the QM calculation, increasing the number of solvent displacements which do not require calculations that update the solute wave function will produce a large improvement in the overall performance of the method. Analyzing the accuracy and efficiency of the new procedure is the focus of this article. Results on the  $\text{Na}^+(\text{H}_2\text{O})_n$  ( $n = 6, 14, 125$ ) systems will be reported. Furthermore, in previous articles we have provided a theoretical basis and systematic assessment of the accuracy of the perturbative MC method.<sup>11,12</sup> No attempt was made to investigate the accuracy of the calculated solvent structure using this approach. We therefore present in this article radial distribution functions (rdf's) obtained for the different  $\text{Na}^+(\text{H}_2\text{O})_n$  systems.

## Theoretical Background

Details concerning the theoretical background for the combined QM/MM method have been described previously.<sup>6–9</sup> For a solution, the effective Hamiltonian describing the system can be separated into three terms:

$$\hat{H}_{\text{eff}} = \hat{H}_U^0 + \hat{H}_{U-V} + \hat{H}_{V-V} \quad (1)$$

where  $\hat{H}_U^0$  is the portion of the effective Hamiltonian that describes the solute molecule which has a QM, *in vacuo*, representation.  $\hat{H}_{U-V}$  is the solute-solvent interaction Hamiltonian, and  $\hat{H}_{V-V}$  is the Hamiltonian describing interactions between solvent molecules in the MM region. As far as the perturbative MC<sup>11,12</sup> approach is concerned, the portion of the effective Hamiltonian that is of

interest is  $\hat{\mathbf{H}}_{U-V}$ , and is given by:

$$\hat{\mathbf{H}}_{U-V} = \sum_i \sum_{\alpha} -\frac{q_{\alpha}}{R_{i\alpha}} + \sum_A \sum_{\alpha} \frac{q_{\alpha} Z_A}{R_{A\alpha}} + \sum_A \sum_{\alpha} \left( \frac{A_{\alpha A}}{(R_{\alpha A})^{12}} - \frac{B_{\alpha A}}{(R_{\alpha A})^6} \right) \quad (2)$$

where the first two terms represent electrostatic interactions between the solvent interaction sites, and the solute electrons and nuclei, respectively. The last term describes the dispersion or van der Waals interactions between solute and solvent. The indices  $i$  and  $\alpha$  run over the electrons in the QM region, and the interaction sites on each of the MM molecules, respectively, while index  $A$  runs over the nuclei in the quantum region.

The total energy for the solvated system is expressed as:

$$E_{\text{tot}} = \langle \Psi | \hat{\mathbf{H}}_U^0 + \sum_i \sum_{\alpha} -\frac{q_{\alpha}}{R_{i\alpha}} | \Psi \rangle + \sum_A \sum_{\alpha} \frac{q_{\alpha} Z_A}{R_{A\alpha}} + E_{U-V}^{\text{vdW}} + E_{V-V} \quad (3)$$

where the first term is the expectation value of the portions of the effective Hamiltonian, which are functions of the electronic coordinates; the second term is the contribution to the total energy that arises due to interactions between the solute nuclei and the solvent interaction sites; the third term describes the dispersion interactions between the solute and the solvent; and the last term is the energy that arises from interactions between classical solvent molecules in the MM region.

Using the perturbative MC approach,<sup>11</sup> the main concern is with the changes in  $\hat{\mathbf{H}}_{\text{eff}}$  that occur corresponding to a change in the position or orientation of a solvent molecule due to an accepted MC step. Specifically, it is the portion of the effective Hamiltonian that describes interactions between electrons in the QM solute and the interaction sites of the classical solvent molecules, that is of interest. When a solvent molecule  $m$  is displaced, this portion of  $\hat{\mathbf{H}}_{\text{eff}}$  takes the form:

$$\Delta H = \sum_i \sum_{\alpha \in m} -q_{\alpha} \left( \frac{1}{R'_{i\alpha}} - \frac{1}{R_{i\alpha}} \right) \quad (4)$$

If the perturbation given by eq. (4) is small, the energy change corresponding with the displacement of solvent molecule  $m$  can be approximated

within first-order perturbation theory by:

$$\langle \Psi | \sum_i \sum_{\alpha \in m} -q_{\alpha} \left( \frac{1}{R'_{i\alpha}} - \frac{1}{R_{i\alpha}} \right) | \Psi \rangle \quad (5)$$

where  $\Psi$  is the solute wave function from the previously accepted full SCF MC step. The change in the total energy for such a perturbative MC step can be expressed as:

$$\Delta E_{\text{tot}} = \sum_{\mu\nu} P_{\mu\nu} \langle \mu | \sum_{\alpha \in m} -q_{\alpha} \left( \frac{1}{R'_{i\alpha}} - \frac{1}{R_{i\alpha}} \right) | \nu \rangle + \sum_A \sum_{\alpha} q_{\alpha} Z_A \left( \frac{1}{R'_{A\alpha}} - \frac{1}{R_{A\alpha}} \right) + \Delta E_{U-V}^{\text{vdW}} + \Delta E_{V-V} \quad (6)$$

where  $P_{\mu\nu}$  is the density matrix element between the basis functions  $|\mu\rangle$   $|\nu\rangle$ , and  $\Delta E_{U-V}^{\text{vdW}}$  and  $\Delta E_{V-V}$  are the changes in the solute-solvent dispersion energy and solvent-solvent interactions, respectively. Eq. (6) indicates that the main computational cost associated with calculating  $\Delta E_{\text{tot}}$  is the evaluation of  $m \times k$  number of one-electron integrals, where  $k$  is the number of basis functions. The perturbative MC approach thus leads to a significant reduction in the computational expense, relative to performing a full SCF calculation at each displacement of a solvent molecule. Updating the solute wave function, through the performance of a full SCF calculation, needs to occur only after a certain number of perturbative moves to avoid accumulation of errors.

The question that needs to be addressed is, "What is the maximum number of perturbative moves that can be performed between SCF calculations before accumulating an error exceeding a given limit?" To answer this, we define the error function:

$$\text{Error} \equiv E(P_{\mu\nu}^{\text{previous}}) - E(P_{\mu\nu}^{\text{current}}) \quad (7)$$

where the first term is the energy obtained using a density matrix from the SCF calculation corresponding to the previously accepted MC displacement of a solvent molecule, and the second energy term is the energy that would be obtained if the density matrix was calculated for the current configuration of solute and solvent. This error should decrease sharply as a function of the distance between the QM solute and the MM solvent molecule being displaced during an MC step. This distance dependence can be approximated using classical electrostatics by recalling the formula for the elec-

tric field generated by a solute molecule, at some point in space where a classical, MM solvent molecule resides:

$$\vec{F} = \sum_{i=1}^N \frac{q_i}{r_i^3} \vec{v}_i \quad (8)$$

where  $r$  is the distance between the solute species and the solvent molecule, and  $\vec{v}_i$  is the unit vector oriented along this distance. The dipole experienced by a solvent molecule in the presence of this field can be calculated by taking the vector product of the expression for the electric field and  $\tilde{\alpha}$ , the polarizability of the solvent molecule:

$$\vec{\mu} = \tilde{\alpha} \cdot \left( \sum_{i=1}^N \frac{q_i}{r_i^3} \vec{v}_i \right) \quad (9)$$

The energy that arises due to the polarizing effect of some configuration of solvent molecules is given by:

$$E_{\text{pol}} = -\frac{1}{2} \left( \sum_{i=1}^N \frac{q_i}{r_i^3} \vec{v}_i \cdot \left( \tilde{\alpha} \cdot \sum_{i=1}^N \frac{q_i}{r_i^3} \vec{v}_i \right) \right) \quad (10)$$

which is the expression for the electric field given by eq. (8) dotted into the dipole moment given by eq. (9) and multiplied by a factor of  $-1/2$ .

The error described by eq. (7) is nothing more than the change in the total energy due to the change in the position of an MM solvent molecule.

$$\text{Error} = \frac{\Delta E}{\Delta r} \quad (11)$$

Applying this idea to eq. (11), and taking the limit of the change in the energy as the change in  $r$  goes to zero, we have an approximate expression for the distance dependence of the error:

$$\text{Error} \propto \frac{1}{r^7} \quad (12)$$

This expression for the error gives the distance dependence for the function used for the weighting of the displacements of individual solvent molecules. Due to the short-range nature of this error weighting function, it is not very sensitive to the type of solute. Thus, for a given solvent type, we use a simple fitting procedure as given in what follows to obtain the coefficient for this function. First, we perform calculations for the interaction of an *ab initio*  $\text{Li}^+$  with an empirical TIP3P<sup>15</sup> water molecule, in which the exact error defined in eq. (7) was obtained. The relative geometries of the

$\text{Li}^+$  and the  $\text{H}_2\text{O}$  molecules were  $\text{C}_{2v}$ ,<sup>16</sup> with the  $\text{Li}^+$  nearest to the O atom of the  $\text{H}_2\text{O}$ , and the  $\text{H}_2\text{O}$  rotated  $45^\circ$  in the plane of the  $\text{Li}^+$  and  $\text{H}_2\text{O}$ , relative to this  $\text{C}_{2v}$  geometry. A least-squares fit to a function, which has the general  $r^{-7}$  form, was then performed. In actual application, this error is allowed to accumulate until it passes a given limit, at which point a full SCF calculation is then performed. This procedure was implemented into our local interface between G92/DFT<sup>17</sup> and Boss 3.6.<sup>18</sup>

## Computational Details

To test the performance of the new procedure, a series of QM/MM simulations were carried out on the  $\text{Na}^+(\text{H}_2\text{O})_n$  ( $n = 6, 14, 125$ ) systems. In this study, no solute displacements were performed and no changes in the volume were allowed. For systems that require displacing the solute or changing the volume, full SCF calculations must be performed corresponding to either scenario. Using the error defined in eq. (7), an error limit of 0.01 kcal/mol was allowed to accumulate between full SCF calculations. Simulations were performed at  $25^\circ\text{C}$  and 1 atm. Metropolis sampling was used in all simulations and, with the 125 water system, preferential sampling<sup>19</sup> was used with  $1/(r^2 + \text{WKC})$  weighting, where  $\text{WKC} = 100$ . For the 125-water-molecule case, a solute-solute interaction cutoff distance of 10.0 Å was used.

$\text{Na}^+$  was treated quantum mechanically at the HF, MP2, and DFT levels using the 6-31G\* basis set. For the DFT representation we used the combination of the nonlocal Becke<sup>20</sup> exchange, and the Lee–Yang–Parr<sup>21</sup> correlation functionals.

All solvent  $\text{H}_2\text{O}$  molecules were treated by the three-site TIP3P model ( $d = 0.9572$  Å,  $\alpha = 104.52^\circ$ ). Although empirical parameters exist for the  $\text{Na}^+$ , which have been used successfully in many MM simulations, it has been understood that new van der Waals parameters must be fitted for use in QM/MM simulations. However, no error analysis was given for the common practice<sup>8</sup> of using MM van der Waals parameters for solute in QM/MM simulations. To gain some insight into the results obtained with the use of different vdW parameters for  $\text{Na}^+$  in QM/MM simulations, the empirical OPLS parameters<sup>22</sup> were used, as well as the values reported by Freindorf and Gao,<sup>23</sup> which were fitted for use in *ab initio* QM/MM simulations.

For each cluster, standard 1.0 M configuration MC simulations were performed to equilibrate the

system. Our Gaussian/BOSS interface, including the implemented weighting functions, was used to run the simulations, with  $2.0 \times 10^5$  configurations sampled for averaging. The average number of water displacements that occurred between the SCF portion of the simulation was calculated to illustrate the increase in the efficiency that is experienced for different clusters, while maintaining an error accumulation below 0.01 kcal/mol in total electronic energy.

Results and Discussion

Average numbers of solvent displacements between successive SCF calculations for the different QM methods and vdW values are shown in Table I. The distance dependence of the error defined by eq. (7) is illustrated by the increasing number of average moves, mean NMOVE, as the number of water molecules increases. For all three systems, the OPLS vdW values give mean NMOVE values that are smaller than the results obtained using the Gao values for the same QM method and cluster size. Due to the fact that the vast majority of the computational demand associated with the QM/MM method involves SCF calculations of the QM portion of the simulation, the data in Table I represent, qualitatively, the increase in the efficiency that the weighting functions provide in connection with the perturbative MC method. While this increase in efficiency is relative to a simulation in which the performance of SCF calculations occurs with each displacement of a solvent molecule, it is important to make a few points. First, the use of perturbation theory to improve the efficiency of QM/MC simulations has also been demonstrated in our earlier studies and in the work of Tunon et al.<sup>14</sup> and Gao.<sup>13</sup> These studies involve a much larger number of SCF calculations, which update the electron density of the solute region. For exam-

ple, Tunon imposed conditions to the simulation to assure that no more than 10 MC steps were made between the DFT calculations. While this also increases the efficiency of the simulation relative to performing the SCF calculation with each step, it does not allow for the performing of an “optimal” number of MC moves. The weighting functions allow for over 100 solvent displacement in a water cluster consisting of six water molecules. Even with a cluster of this small size, many more perturbative steps can be carried out, without introducing large amounts of error.

The binding enthalpies ( $\Delta H_{\text{bind}}$ ) for the  $\text{Na}^+(\text{H}_2\text{O})_6$ ,  $\text{Na}^+(\text{H}_2\text{O})_{14}$ , and  $\text{Na}^+(\text{H}_2\text{O})_{125}$  systems are listed in Table II. The  $\Delta H_{\text{bind}}$  values obtained using the OPLS values for the vdW parameters for the solute-solvent interactions are too negative for both the  $\text{Na}^+(\text{H}_2\text{O})_6$  and  $\text{Na}^+(\text{H}_2\text{O})_{14}$  systems, when compared with standard MC results published by Jorgensen and Severance,<sup>24</sup> and with corresponding experimental values.<sup>25</sup> No MM or experimental data are available for  $\text{Na}^+$  solvated by a cluster consisting of 125 water molecules.

The different results for the use of the OPLS and Gao values for the vdW parameters illustrate some important points. Because MM simulations do not represent electrons on either the solute or solvent species explicitly, these MM force field parameters

TABLE I. Average Number of Solvent Displacements, Mean NMOVE, for  $\text{Na}^+(\text{H}_2\text{O})_n$ .

QM / vdW	$\text{Na}^+(\text{H}_2\text{O})_6$	$\text{Na}^+(\text{H}_2\text{O})_{14}$	$\text{Na}^+(\text{H}_2\text{O})_{125}$
HF / Gao	135	280	2221
HF / OPLS	103	217	1332
MP2 / Gao	141	285	1999
MP2 / OPLS	103	211	1665
DFT / Gao	135	284	
DFT / OPLS	105	218	

TABLE II. Enthalpies of Binding –  $\Delta H_{\text{bind}}$  for  $\text{Na}^+(\text{H}_2\text{O})_6$  and  $\text{Na}^+(\text{H}_2\text{O})_{14}$  Clusters.

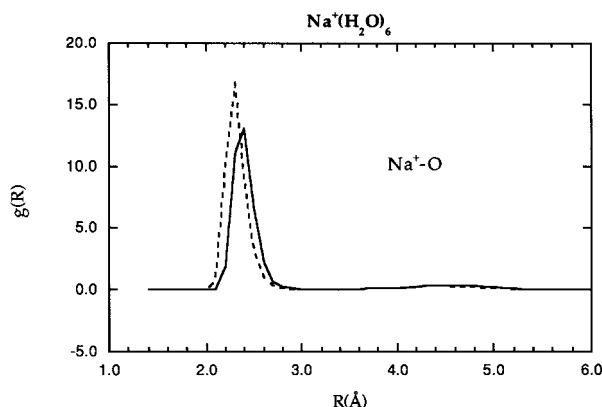
Method	Gao parameters	OPLS parameters
$\text{Na}^+(\text{H}_2\text{O})_6$		
HF	103.8 <sup>a</sup>	112.8
MP2	102.7	113.0
DFT	104.2	112.0
Monte Carlo / OPLS <sup>b</sup>	105.5	
Experiment <sup>c</sup>	96.4	
$\text{Na}^+(\text{H}_2\text{O})_{14}$		
HF	175.9	184.4
MP2	172.3	184.0
DFT	173.3	185.1
Monte Carlo / OPLS <sup>b</sup>	177.4	
$\text{Na}^+(\text{H}_2\text{O})_{125}$		
HF	1016.2	1054.3
MP2	980.2	1073.0

<sup>a</sup>All binding enthalpies are in kcal / mol.  
<sup>b</sup>Ref. 23. The reported uncertainties in  $\Delta H$  are  $\pm 0.3$  kcal / mol.  
<sup>c</sup>Ref. 24.

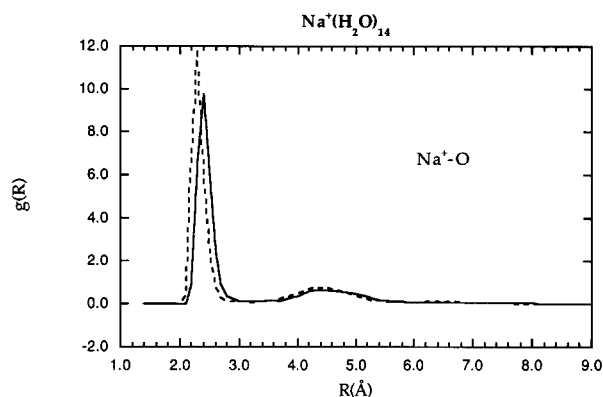
are not acceptable for use in a QM/MM simulation. The QM/MM representation allows for the polarization of the solute region in the presence of the field generated by the solvent molecules. This contribution to the total interaction energy is double counted when OPLS parameters are used in a QM/MM simulation. Therefore, using the OPLS values gives results that describe  $\text{Na}^+$ -water clusters that have inaccurately too strong  $\Delta H_{\text{bind}}$ , correspondingly short solvent-solvation shell distances, and lower values for the average number of solvent displacements between SCF calculations. The latter of these results is evidence of the tighter packing of all of the water molecules around the  $\text{Na}^+$ .

The solvent structures surrounding the  $\text{Na}^+$  are illustrated by the rdf's of Figures 1–3. Rdf's obtained for the different levels of quantum theory and similar vdW values give similar results and, for this reason, Figures 1–3, which show results from the MP2 representation of the solute, are given as an illustration of the results for all the different representations of  $\text{Na}^+$ .

Figures 1–3 show comparisons of the rdf's obtained using the Gao and OPLS parameters for the  $\text{Na}^+(\text{H}_2\text{O})_6$ ,  $\text{Na}^+(\text{H}_2\text{O})_{14}$ , and  $\text{Na}^+(\text{H}_2\text{O})_{125}$  systems. The position of the first maximum obtained using the Gao parameters for all  $\text{Na}^+(\text{H}_2\text{O})_n$  systems compares favorably to results obtained using classical simulation techniques for the same  $\text{Na}^+-\text{H}_2\text{O}$  cluster size,<sup>26</sup> and for dilute solutions of  $\text{Na}^+$  in  $\text{H}_2\text{O}$ .<sup>27</sup> Specifically, for the  $\text{Na}^+(\text{H}_2\text{O})_{125}$



**FIGURE 1.** Calculated  $\text{Na}^+-\text{O}$  radial distribution function for  $\text{Na}^+(\text{H}_2\text{O})_6$  cluster. For all figures, the  $\text{Na}^+$  is represented at the MP2 level of theory, and the dashed line represents the rdf obtained using the OPLS values for the vdW parameters. The solid line represents the results obtained using the Gao values. The reference density for the rdf's is the bulk density.

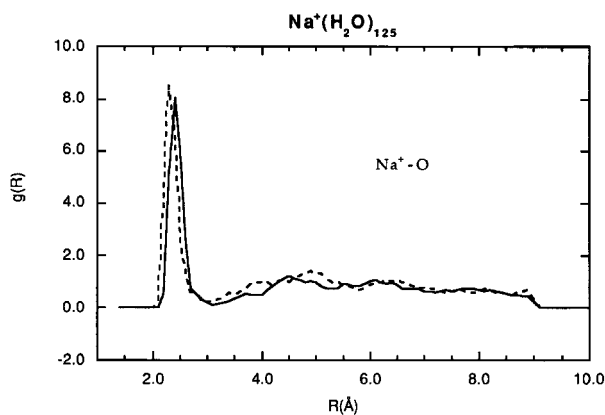


**FIGURE 2.** Calculated  $\text{Na}^+-\text{O}$  radial distribution function for  $\text{Na}^+(\text{H}_2\text{O})_{14}$  cluster.

system, the position of the first peak calculated with the Gao parameters agrees much better with experimental values,<sup>28</sup> which were reported to be 2.38 and 2.4 Å, than do the results obtained using the OPLS parameters. The Gao results also compare favorably with values obtained from classical simulation techniques, which range from 2.29 to 2.35 Å.<sup>29</sup>

## Conclusions

It has been demonstrated that use of the perturbative MC method with an error weighting function can increase the efficiency of QM/MM simulations. The increase in the efficiency is greater for systems consisting of larger numbers of solvent molecules due to the distance dependence of the weighting function. The mean NMOVE values illustrate this increase in efficiency for the



**FIGURE 3.** Calculated  $\text{Na}^+-\text{O}$  radial distribution function for  $\text{Na}^+(\text{H}_2\text{O})_{125}$ .

$\text{Na}^+(\text{H}_2\text{O})_n$  systems of different size. This increase in efficiency will allow for the investigation of processes of increased size and computational rigor. In the future, we intend to use this approach to investigate more complex systems. This increase will also make it possible to move away from classical representations of the solvent, which are the result of fitting parameters to empirical data and toward more rigorous representations such as the effective fragment potential (EFP).<sup>30</sup>

We caution against the use of MM vdW parameters in QM/MM simulations. In QM/MM simulations, where the QM solute is allowed to be polarized, using MM force fields will double count these interactions. This will overestimate binding enthalpies, with corresponding solvation shells that have small distances between solute and solvent.

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